BIOMOD LABS · RESEARCH PEPTIDE CO.

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Cagrilintide

A long-acting amylin analogue engineered by Kruse and colleagues at Novo Nordisk — built on the human amylin backbone with calcitonin-inspired structural elements, fibrillation-resistance proline substitutions, and an N-terminally attached C20 fatty diacid for reversible albumin binding.

DEVELOPMENT CODE	CATALOG REFERENCE	CLASS	DATE OF ISSUE
NN9838 · AM833	BM-LYO-004	Synthetic peptide · 37 a.a. + C20 diacid	May 2026

Cagrilintide is a long-acting synthetic analogue of the pancreatic hormone amylin, engineered at Novo Nordisk by Kruse, Hansen, Dahl, Schäffer and colleagues (J Med Chem, 2021, PMID 34288673). The molecule is built on the human amylin backbone with four chemistry modifications addressing the principal challenges of amylin pharmacology: (a) ***14E/17R substitutions*** *that stabilise the central α-helix via an introduced salt bridge; (b)* ***25P/28P/29P substitutions*** *(drawn from rat amylin) that reduce β-sheet propensity and dramatically lower the molecule's fibrillation tendency; (c) a* ***C-terminal proline*** *that improves calcitonin receptor (CTR) potency; and (d) an* ***N-terminally linked C20 fatty diacid*** *that confers reversible non-covalent association with serum albumin and the extended duration of action characteristic of the molecule. Receptor pharmacology at the amylin receptor complexes (AMY1R, AMY3R) and the parent calcitonin receptor (CTR) is preserved despite the chemistry modifications.* ***This monograph summarises published cellular pharmacology and preclinical findings for laboratory research reference only.***

01 Compound Profile

COMMON DESIGNATION	Cagrilintide · AM833 · NN9838
BACKBONE	Human amylin (37 a.a.) with 14E/17R salt-bridge, 25P/28P/29P fibrillation-resistance, and C-terminal proline substitutions
SIDE-CHAIN MODIFICATION	N-terminal acylation with C20 eicosanedioic acid (fatty diacid) for reversible albumin binding
MOLECULAR MASS	~3800 g · mol^{-1} (approximate, depending on counter-ion)
PRIMARY MOLECULAR TARGETS	Amylin receptor type 1 (AMY1R, CTR+RAMP1) · Amylin receptor type 3 (AMY3R, CTR+RAMP3) · Calcitonin receptor (CTR) — all Class B GPCR / RAMP heterodimer complexes; full agonist[1]
PHYSICAL FORM	White lyophilised solid
SOLUBILITY (LAB RECONSTITUTION)	Soluble in sterile water for injection; the lipid side chain creates surfactant-like behaviour; gelling behaviour has been reported on rapid reconstitution at high concentration — reconstitute slowly with gentle mixing
STORAGE (RESEARCH HANDLING)	Lyophilised solid: −18 °C, desiccated; reconstituted solution refrigerated 2–8 °C; long-term aliquots at −18 °C; fibrillation susceptibility minimised relative to native amylin but not eliminated — avoid agitation, mechanical shear, and prolonged room-temperature solution storage
CRITICAL CHEMISTRY NOTE	Cagrilintide retains the Cys2-Cys7 disulfide of native amylin; reducing agents must be avoided. The C-terminal amide is essential for receptor binding[1]
ANALYTICAL SPECIFICATION	≥ 98 % purity by HPLC (BIOMOD Labs internal release specification)

02 Origin and Chemistry

The chemistry challenge addressed by the cagrilintide design programme is one of the most distinctive in peptide drug discovery: native human amylin has an exceptionally high propensity for amyloid fibril formation — a property closely linked to type-2-diabetes pathology in human pancreatic islets, where amylin-derived amyloid deposits are a hallmark histological feature. The pre-existing amylin analogue pramlintide partially addressed this

liability by introducing rat-amylin-derived proline substitutions in the central β-sheet-forming region, but pramlintide retains a short plasma half-life requiring thrice-daily injection. The cagrilintide design objective was a once-weekly long-acting amylin analogue with substantially reduced fibrillation propensity.[1]

The Kruse et al. 2021 SAR programme systematically explored four chemistry axes: (a) *helix-stabilising mutations* — the 14E/17R pair introduces a salt bridge predicted to stabilise the central amphipathic α-helix that engages the receptor's TM domain; (b) *fibrillation-resistance mutations* — three proline substitutions at positions 25, 28, and 29, derived from the natively non-fibrillating rat amylin sequence; (c) *C-terminal modifications* — the C-terminal proline addition improves CTR potency specifically; and (d) *lipidation chemistry* — systematic exploration of fatty acid length and linker chemistry identified N-terminal C20 fatty diacid attachment as optimal for albumin binding combined with preserved receptor potency. The resulting molecule retains the Cys2-Cys7 disulfide of native amylin (essential for the receptor-engaging fold) and the C-terminal amide (essential for AMY3R/CTR binding).[1]

03 Molecular Targets and Cellular Signalling

Cagrilintide engages the amylin receptor system — a family of heterodimeric receptor complexes formed by the calcitonin receptor (CTR) combined with receptor activity-modifying proteins (RAMP1, RAMP2, or RAMP3). The principal physiological amylin receptors are AMY1R (CTR + RAMP1), AMY2R (CTR + RAMP2), and AMY3R (CTR + RAMP3); cagrilintide binds AMY1R and AMY3R with full agonist activity and additionally engages the parent CTR. Receptor activation couples to Gαs in cell-line transfection systems, with downstream cAMP elevation, PKA activation, and CREB phosphorylation. In hindbrain area-postrema neurons — a principal site of physiological amylin action — receptor activation drives signalling that contributes to satiety and reduced food intake.[1,4]

A 2025 study by Carvas, Leuthardt, Kulka and colleagues published in *EBioMedicine* used genetic knockout models to demonstrate that cagrilintide's body-weight effects in mice are mediated specifically through brain AMY1R and AMY3R receptors, with the hindbrain identified as a critical anatomical locus for the molecule's central action.[4] PRECLINICAL · MOUSE

04 Preclinical Findings

SYSTEM	PREPARATION	REPORTED OBSERVATION	REF.
Receptor activation	CHO cells transfected with hAMY3R, hCTR	Full agonism at AMY3R and CTR; balanced potency profile	1
Fibrillation resistance	Aqueous solution stability assays	Substantially reduced fibrillation tendency vs. native amylin and pramlintide	1
Albumin binding	Cell-free binding studies	Reversible non-covalent binding via C20 diacid; extended plasma residence	1
Body weight in obese rodents	Diet-induced obese rat / mouse models	Reduction in body weight and food intake	1
Central nervous system action	Hindbrain-targeted knockout mice (AMY1R/AMY3R)	Body-weight effects require brain AMY1R/AMY3R signalling	4

SYSTEM	PREPARATION	REPORTED OBSERVATION	REF.
Optimised analogue NN1213	Cell-line and animal characterisation	2024 Kruse et al. paper describes follow-on optimised amylin analogue NN1213	2

05 Research Synthesis & Limitations

METHODOLOGICAL NOTES

Cagrilintide is among the more thoroughly characterised research peptides in the amylin family, with detailed published SAR documenting the four chemistry-modification axes, receptor pharmacology at AMY1R/AMY3R/CTR, and animal-model body-weight pharmacology. For researchers, the principal handling considerations are (a) the molecule retains some residual fibrillation susceptibility despite the proline substitutions — agitation, mechanical shear, and prolonged room-temperature storage in solution should be avoided; (b) the Cys2-Cys7 disulfide is essential and reducing agents (DTT, β-mercaptoethanol, TCEP) must be excluded; and (c) at high reconstitution concentrations gelling behaviour has been reported, so slow reconstitution with gentle mixing is preferred over vortexing.

06 Laboratory Handling, Reconstitution, and Storage

Lyophilised cagrilintide is supplied under research-use specifications and held at −18 °C, desiccated. Reconstitution in sterile water for injection is the standard practice; the molecule is moderately water-soluble. **Reconstitute slowly with gentle mixing** — vortexing or rapid solubilisation at high concentration can produce gelling. The lipid side chain creates surfactant-like behaviour at dilute concentrations; siliconized glass or polypropylene tubes are preferred. **The Cys2-Cys7 disulfide must be preserved** — reducing agents must be excluded from buffers, vehicles, and laboratory glassware. Reconstituted solutions are held refrigerated 2–8 °C for short-term work; long-term aliquoted storage at −18 °C with strict minimisation of freeze–thaw. Working concentrations are determined by the investigator's experimental design.

07 References

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